and agglomerates to exist within a cluster of microparticles. Thus there are clear differences between the two and both are used correctly in claim 1.

In addition to revising the claims to be more precise, appropriate Markush terminology is used in claim 3, the transcription error in claim 4 is remedied and the various preferred aspects of original claim 9 made the subject of further dependent claims 12-13.

Original claims 1, 3-4, 6, 9 and 10 are rejected as allegedly being anticipated by U.S. Patent No. 5,631,023 to Kearney. A closer review of the actual disclosure in this document will reveal that applicants' claimed rapidly dispersing solid therapeutic dosage forms are not described or anticipated by the disclosures of this document and, in fact, important requirements of applicants' claims are nowhere included in the content of the documents cited. The Kearny patent describes a method of "preparing a rapidly dispersing pharmaceutical tablet of a granular therapeutic agent which has both relatively low solubility and relatively large particle size" (Abstract, sentence 1) -- "1 to 400 microns" (column 10, line 56). Further, Kearny's process is said to be "particularly useful in relation to medicaments whose particle size and weight cause them to settle out of suspension relatively quickly" (column 5, lines 48-51). "Within this understanding,...the average particle size of the medicament particle is generally grater than about 50 micrometers. In the preferred form, the particle size...is between about 5 micrometers and about 400 micrometers" (column 5, lines 61-67).

The present invention relates to compositions of rapidly dispersing formulations containing much smaller (micro) particles of an insoluble drug that are coated with a surface modifier; the particles are in the range of 005 to 10 micrometers. Further, a bulking/releasing matrix is included such that on dispersion the individual microparticles were obtained without significant aggregation or agglomeration of the particles. The problem of aggregation and agglomeration is illustrated in Example 1 of the present application. On the other hand, Kearny's disclosure relates to larger particles – they are *non*-surface modified particles of a drug of low solubility. Kenny does not address the

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problem of aggregation on drying of microparticles, i.e., surface modified particles of an insoluble drug in the size rang of 0.05 to 10 micrometers.

For the above reasons, it is submitted that the rejected claims define subject matter that is distinct from the disclosures of this document. Reconsideration is requested.

Original claims 1-4, 6 and 8-10 are rejected as allegedly being anticipated by U.S. Patent No. 5,976,577 to Green et al. The Green patent relates to "coarse particles...up to a size of 1 millimeter, although the size is generally up to about 500 µm, for example 75 to 400µm, more usually in the region of about 100-300 µm. In this size range, it is possible to apply a uniform intact coating on the particle to achieve freeze dried dosage forms with slow drug release rate." The technique of coating particles to control release rate of the drug is well established technology (Remington Pharmaceutical Sciences, p 1645, reference attached).

On the other hand, in the case of the microparticles as described and claimed in the present application, the surface of the insoluble drug particle is coated with a surface modifier to allow formation and stabilization of microparticles in the range of 0.05 to 10 µm (Pace et al -- Pharmaceutical Technology, March 1999, p. 120 -- reference attached). This coating or surface modification process is quite distinct form that referred to by Green and does not confer any delayed release of the drug as Green requires the present application. As with Kearny Green neither anticipates of renders obvious the subject matter of the new and amended claims now under consideration.

In items 7 and 8 of the Official Action, the examiner is focused on claims 5 and 7 which claims add further aspects and details to the claims from which they depend. Additional secondary references are cited and applied. Again this combination of documents fails to suggest the subject matter of applicant's claims as above amended.

Applicants regard claims 5 and 7 to be patentable over the disclosures of these additional documents for the same reasons that the claims from which claims 5 and 7 depend are patentable over the art cited in items 4 and 5 of the Official Action. As discussed above, the claimed compositions relate to formulations that disintegrate rapidly to yield microparticles that are not aggregated and remain within their original particle

size of 0.05 to 10 micrometers. The disclosures of Carli, Libby, Green and Kearny do not describe the use of microparticles or refer to the problem of aggregation which the present invention overcomes.

For the above reasons, it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and favorable action are solicited.

Respectfully submitted,

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monohydrated α–lactose. (See Chapter 7 on Crystallization)

3.3 The concept of granules

Some crystalline species, such as silicium, can be prepared as monocrystals with coherent diffraction domains with virtually no defects. This is very rare and solids usually take the form of a series of "granules" or "grains". Each granule is a monolith, i.e., constituted by a single block known as the "crystallite".

The **granule or crystallite** (equivalent definition) may be either monocrystalline or polycrystalline. Monocrystalline granules have simple geometric shapes = cubes, parallelepipeds, plates... with the exception of cubes, they are anisotopic, particularly when they are needle–shaped. All monocrystals are compact (no internal porosity).

Polycrystalline granules (the most common) consist of an association of small monocrystals totally or partially attached by rigid joints. These assemblies are known as **aggregates**. They may have an internal porosity. Microcrystals generally measure less than one micrometer and are often randomly oriented relative to each other. The anisotropic effect presented individually by each monocrystal is therefore doubly reduced, first of all at the granule scale and then at powder scale.

In other cases, the microcrystals or nanocrystals are piled up over each other with an angular shift which may sometimes be constant from one layer to the other which defines turbostratic layers.

Many of the properties of a solid matter are linked to the microstructural state of the crystallites which form the polycrystalline solid, since this state confers on the granules activity and geometric shape which are particularly important in determining properties such as dissolution characteristics, friability, flow properties.

4 FROM GRANULES TO POWDER

4.1 From the aggregate to the agglomerate (Figure 5)

In the aggregate, microcrystals are linked by joints made up of the same bonds as within the crystals themselves. However, aggregates can be linked to each other by cohesion forces of another type than the bridges of the constituent materials. Then the assembly of aggregates becomes an agglomerate.

Fine powders are often agglomerated. When the granules have a mean size of less than about 20 to 40 micrometers, the forces of gravity acting on each grain become negligible compared to the inter–granular attraction forces. Each granule subjected to a mixing or transfer operation is no longer able to respond individually. We are then confronted by a system in which the collective behavior of the granules can be described on the basis of two models.

"Soft" agglomerates are granular units which are readily deformed by the slightest mechanical force (for instance, shear).

"Hard" agglomerates retain their geometrical form and the number of granules constituting them during treatments to which the powder is subjected.

Some authors use the word "particles" to describe aggregates and divided solids which do not contain agglomerates and the word "powders" for agglomerated substances (fine powders).

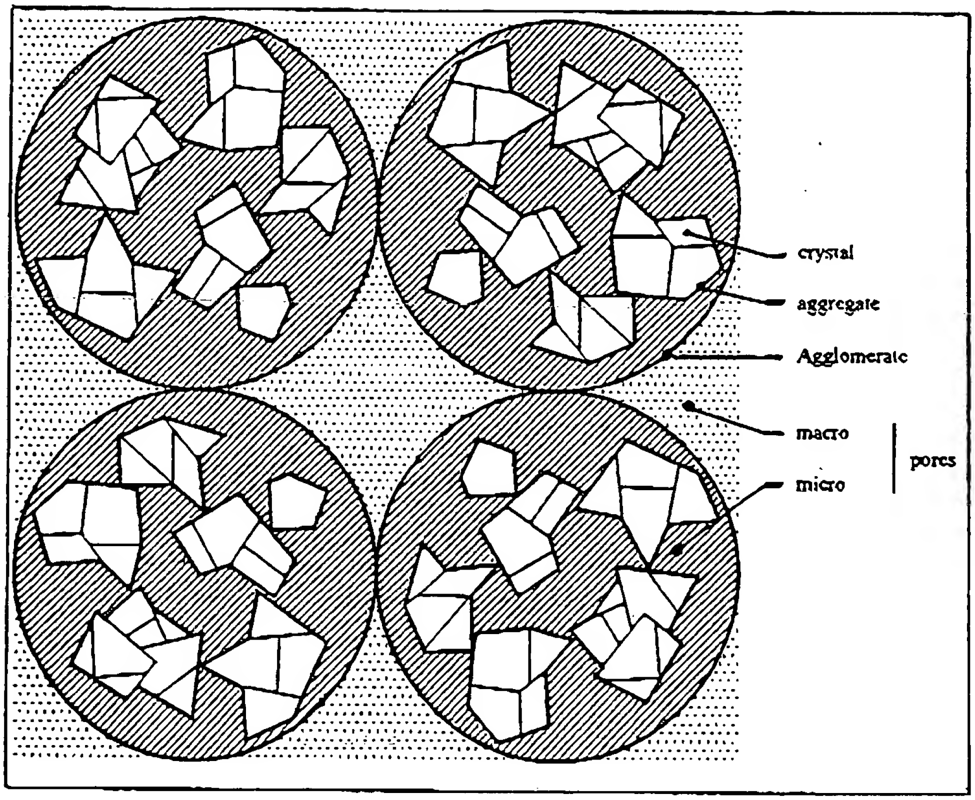


Figure 5 – Powder with agglomeration of aggregates

4.2 Texture

The texture of a powder is the geometric assembly of the grains on a macroscopic scale.

Various parameters are available to characterize this texture, which relate either to the space occupied by grains or the space with no grains (interparticular pores).

The space constituting the pores consists of a gas or liquid phase.

The main geometric parameters of texture are as follows:

– V: the total volume and Vs the volume of solid

– C: the packing fraction, where $C = \dfrac{V_s}{V}$

– e: the porosity, where $e = \dfrac{V - V_s}{V} = 1 - C$

– the size of the grains and agglomerates (if any) and the size of the pores.

– the volume surface area S'_v, the surface area of the solid per unit volume of solid. This surface area can also be calculated per unit apparent volume of the powder (S_v), or

ag·gre·gate (*adj., n.* ag´ri git. -g_t´; *v.* ag´ri g_t´), *adj., n., v.,* **-gat·ed, -gat·ing.**

—*adj.*

1. formed by the conjunction or collection of particulars into a whole mass or sum; total; combined: *the aggregate amount of indebtedness.*
2. *Bot.*
   a. (of a flower) formed of florets collected in a dense cluster but not cohering, as the daisy.
   b. (of a fruit) composed of a cluster of carpels belonging to the same flower, as the raspberry.
3. *Geol.* (of a rock) consisting of a mixture of minerals separable by mechanical means.

—*n.*

4. a sum, mass, or assemblage of particulars; a total or gross amount: *the aggregate of all past experience.*
5. a cluster of soil granules not larger than a small crumb.
6. any of various loose, particulate materials, as sand, gravel, or pebbles, added to a cementing agent to make concrete, plaster, etc.
7. *Math.* set (def. 110).
8. **in the aggregate,** taken or considered as a whole: *In the aggregate, our losses have been relatively small.*

—*v.t.*

9. to bring together; collect into one sum, mass, or body.
10. to amount to (the number of): *The guns captured will aggregate five or six hundred.*

—*v.i.*

11. to combine and form a collection or mass.

[1375–1425; late ME < L *aggreg□tus* (ptp. of *aggreg□re*), equiv. to *ag-* AG- + *greg-* (s. of *grex* flock) + *-□tus* -ATE[1]]

—ag·gre·ga·ble (ag´ri gə bəl), *adj.*

—ag´gre·gate·ly, *adj.*

—ag´gre·gate·ness, *n.*

—ag·gre·ga·to·ry (ag´ri gə tôr´ē, -tōr´ē), *adj.*

—**Syn.** 1. added, complete, whole. 9. assemble, amass, accumulate, gather.

ag·glom·er·ate (*v.*ə glom´ə r_t′; *adj.*, *n.*ə glom´ər it. -ə r_t′), *v.*, **-at·ed, -at·ing,** *adj.*, *n.*

—*v.t.*, *v.i.*

1. to collect or gather into a cluster or mass.

—*adj.*

2. gathered together into a cluster or mass.

3. *Bot.* crowded into a dense cluster, but not cohering.

—*n.*

4. a mass of things clustered together.

5. rock composed of rounded or angular volcanic fragments.

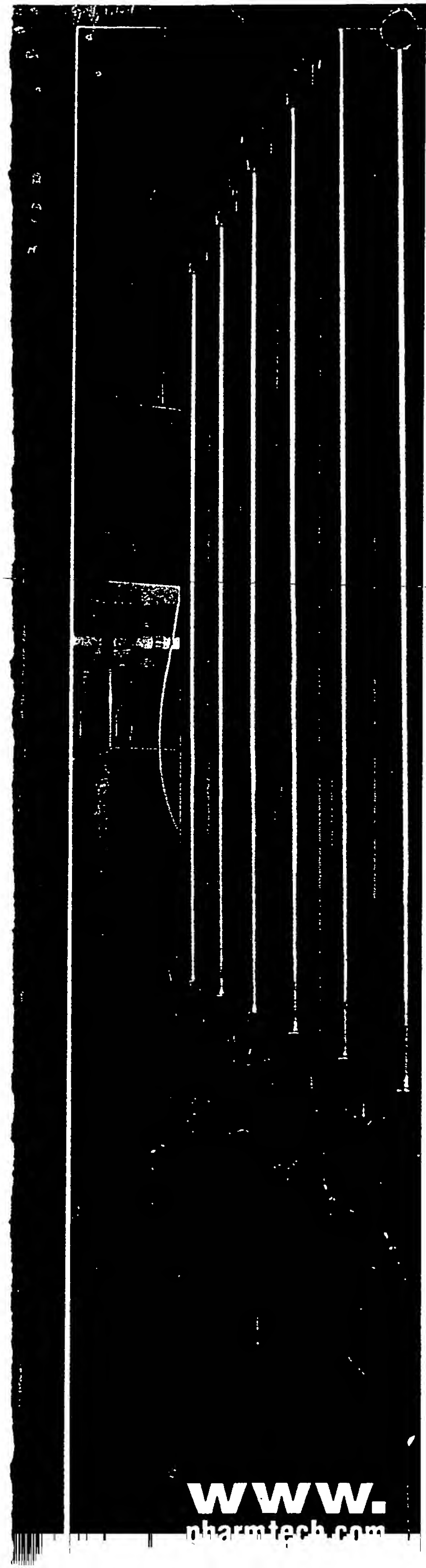
[1675–85; < L *agglomer□tus* (ptp. of *agglomer□re*), equiv. to *ag-* AG- + *glomer-* (s. of *glomus* ball of yarn) + -*□tus* -ATE[1]]

—ag·glom·er·a·tive (ə glom´ə r¯ ′tiv, -ər ə tiv), *adj.*

—ag·glom´er·a′tor, *n.*

—**Syn.** 1. assemble, amass, accumulate.

—**Ant.** 1. disperse, scatter.



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ARTICLES

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Novel Injectable Formulations of Insoluble Drugs

Sarah N. Pace, Gary W. Pace, Indu Parikh, and Awadhesh K. Mishra*

PHOTODISC, INC.

The delivery of water-insoluble or poorly soluble drugs by injection is a recalcitrant problem facing pharmaceutical scientists. Traditional approaches to formulating water-insoluble drugs involve the use of solubilizing agents, detergents, or extreme pH solutions that can significantly increase the toxicities of products. The authors describe a novel drug delivery system for injectable formulations of water-insoluble drugs in which phospholipids are used as a surface-modifying and stabilizing agent to form micron- or submicron-sized particles of a solid or oily drug. Such formulations are readily bioavailable and do not increase the inherent toxicity of the drug.

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*To whom all correspondence should be addressed.

A major problem in the formulation of many injectable drugs is the poor solubility or insolubility of the drug in water. More than one-third of the drugs listed in the *United States Pharmacopeia* fall into these categories. Drug insolubility can delay or completely block new drug development and can prevent the much-needed reformulation of some currently marketed drugs. This article describes a novel drug delivery system, Insoluble Drug Delivery (IDD) technology, which has been shown to successfully address the problem of parenteral delivery of water-insoluble drugs. Although the authors briefly compare the attributes of IDD with other parenteral formulation technologies, a comprehensive review of the latter is not intended.

APPROACHES TO WATER-INSOLUBLE DRUG DELIVERY

Water insolubility of injectable drugs has traditionally been addressed by using detergents or by solubilizing the drugs in organic solvents or in solutions with pH outside the physiological range (see Table I) (1,2). For instance, diazoxide (pK_a 8.5) is formulated at pH 11.6 because it is insoluble and less stable in water at a lower pH (3). The pH required to produce a solution dosage form of a water-insoluble drug can be as low as pH 2 for a weak base (e.g., tetracycline) or as high as pH 12 for a weak acid (e.g., dilantin) (1,4). Highly acidic or alkaline pH can damage tissues at the injection site and can even cause extravasation. Sparingly soluble drugs (e.g., diazepam, phenytoin, and digoxin) are known to precipitate in body fluids following injection because, although they are sufficiently soluble in their cosolvent dosage form, they might not be sufficiently soluble in body fluids or in intravenous (i.v.) infusion fluids. Studies have shown that phlebitis can result from dilution-induced precipitation of amiodarone hydrochloride and that an increased incidence of phlebitis is associated with the infusion of large quantities of particulate matter (5,6). Precipitated particles with diameters >7 μm can also occlude the pulmonary capillaries and cause multiple pulmonary infarctions (4).

Some surfactants used as solubilizing agents in parenteral formulations of insoluble drugs have been implicated in un-

Table I: Comparison of alternative approaches to water-insoluble drug delivery.

Formulation Approach	Important Formulation Considerations	Characteristics and Safety Issues
Solubilization — drug is solubilized in a solvent system suitable for parenteral administration		
Dissolution of salt form of drugs: formulation pH much different than physiological pH to allow dissolution in aqueous parenteral medium	• useful for drugs that are less stable or insoluble in water around physiological pH • limited to drugs that can ionize in water • if buffered, then limited by buffer capacity • limited to low drug payload.	• high or low pH (2–5 or 9–12) limits infusion rate and duration • irritation from drug and/or vehicle or drug precipitation • life-threatening drug precipitation may occur after injection or upon dilution in the infusion media • efficacy limited by the drug's interaction with the in vivo environment • local or systemic toxicity and hypersensitivity potential.
Dissolution in organic solvents: A variety of organic solvents have been used to solubilize water-insoluble drugs for parenteral administration. Recently reviewed in references 1 and 2.	• limited to drugs that are soluble in pharmaceutically acceptable organic solvents • limited to low drug concentration	• use of organic solvents limits infusion rate and duration • irritation from drug and/or vehicle or drug precipitation • local or systemic toxicity and hypersensitivity potential • life-threatening drug precipitation may occur after injection or upon dilution in the infusion media • efficacy limited by the drug's interaction with the in vivo environment.
Solubilization in aqueous sufactant vehicles: micelles and mixed micelles using polysorbates, poloxamers, polyethoxylated castor oil, bile salts, etc.	• useful for those water-insoluble drugs that can be dissolved in these surfactant vehicles	• potential of hypersensitivity, toxicity, and/or hemolysis • formula irritation potential • infusion of diluted formula may be required • danger of drug precipitation upon dilution in infusion media • efficacy limited by the drug's interaction to the in vivo environment.
Solubilization upon complexation: molecular complex of drug with vehicle that is water-soluble, e.g., β-cyclodextrin	• good stability • limited to those drugs that can form these complexes	• drug binding to β-cyclodextrin is equilibrium driven, and upon dilution and/or injection, some or all of the drug may be released and may precipitate • reaction between cyclodextrins and cholesterol can lead to severe nephrotoxicity • formula irritation potential.

desirable biological reactions after injection. For example, researchers have shown that the presence of Cremophor-EL (BASF Corp., Parsippany, NJ) (polyethoxylated castor oil) in an i.v. injection can cause anaphylaxis (7–10). Similarly, Tween-80 (ICI Surfactants, Wilmington, DE) (a polysorbate) is known to cause hypotension, tachycardia, and a rise in histamine levels (10). Muñoz et al. have reported vasodilatation, hypotension, and bradycardia associated with amiodarone containing Tween-80 in patients undergoing coronary angiography (11).

Since the early 1970s, scientists have searched for injectable drug delivery systems for water-insoluble or poorly soluble drugs that minimize risk and allow the formulation of a stable, sterilized product. Although traditional methods are still widely used, newer approaches — such as the formulation of water-insoluble or poorly soluble drugs in emulsions, liposomes, cyclodextrin–drug complexes, nanospheres, and nano- or microparticles — are progressing toward more ideal drug delivery systems.

Water-insoluble drug delivery systems can be classified into two broad categories: monophasic solutions (solubilization of the salt form, solubilization with organic cosolvents or surfactant vehicles, and solubilization by complexation [e.g., with β-cyclodextrin]) and multiphasic dispersed systems (emulsions, liposomes, nanospheres, and IDD technology). In this article, *nano-* or *microparticles* are defined as micron- or submicron-sized particles that are coated with a surface modifier. The term *nanosphere* is normally considered to identify micron or submicron particles of a drug entrapped in a suitable polymeric matrix.

Although each system has its advantages, characteristic limi-

Table I continued: Comparison of alternative approaches to water-insoluble drug delivery.

Formulation Appr ach	Important F mulati n Consid rati ns	Characteristics and Safety I sues
Dispersed syst ms — drug is solubilized or entrapped in lipophilic vehicle and dispersed in aqueous medium		
Emulsions: oil-solubilized drugs dispersed in an aqueous medium and stabilized with an emulsifier surfactant	∘ low drug payload ∘ only suitable for drugs that dissolve in pharmaceutically acceptable oil	∘ metabolized in a similar way to chylomicrons ∘ long history of clinical use ∘ low toxicity depending on the excipients used ∘ accumulation in the RES can occur depending on the stability in the blood stream and the emulsifier used.
Liposomes: phospholipid unilamellar or multilamellar vesicles	∘ low drug payload ∘ only suitable for drugs that dissolve in the phospholipid bilayers (liposomes)	∘ selectively taken up by the RES, therefore good delivery system for the RES ∘ may be toxic to RES components because of high degree of accumulation in these compartments. ∘ manufacturing process changes may alter efficacy and stability of final product
Nanospheres: solid, colloidal particles, ranging from 100 to 1000 nm, that incorporate the drug through dissolution, encapsulation, or entrapment in artificial or natural polymer matrix	∘ only suitable for drugs that can be incorporated in polymeric matrices ∘ low drug payload that depends on the drug incorporation method	∘ safety depends on the excipients (matrix) used ∘ sterility and difficulty in sterilization ∘ complicated release profile from the matrix ∘ altered pharmacokinetics of the drug, possibility of sustained release ∘ rapidly taken up by the RES, especially liver.
IDD technology (MicroParticle and MicroDroplet formulations): phospholipid encapsulated dispersion of submicron-sized solid or liquid drug particles	∘ high payload ∘ applicable to all water-insoluble, solid or liquid drugs; solubility of the drug in phospholipid is not a limiting factor ∘ good stability	∘ does not alter pharmacokinetics and pharmacodynamics of the drug ∘ not affected by the RES ∘ good efficacy profile ∘ both immediate release (i.v.) and sustained release (intramuscular, subcutaneous, or intradermal) delivery profiles ∘ uses well-established, tissue-compatible excipients of low toxicity ∘ good safety and tolerability.

tations narrow its suitability for formulating certain drugs. For example, the extent to which a water-insoluble drug can be solubilized by complexation with β-cyclodextrin depends on the equilibrium binding properties. Because the binding of drug by β-cyclodextrin is an equilibrium phenomenon, some or all of the drug may be released upon dilution or injection, thereby causing the potential for drug precipitation. Table I shows a brief comparison of alternative approaches for parenteral formulation of water-insoluble and sparingly soluble drugs.

Emulsions, particularly oil-in-water emulsions, are the oldest multiphasic systems for parenteral delivery of water-insoluble drugs and have been reviewed extensively (12,14–16). These systems are stabilized aqueous dispersions of organic liquid droplets (13). The lipophilic, water-insoluble drug remains dissolved in the organic liquid phase that is chosen from pharmaceutically acceptable oils for parenteral administration. Efficacy is therefore limited by drug–oil solubility and the dissolution threshold of the drug in oil.

Although liposomes (uni- or multilamellar vesicles of phospholipid bilayers) are especially suitable for water-soluble drugs, they can be used to deliver water-insoluble, lipophilic drugs because a limited amount of the drug can partition into the phospholipid bilayers. Liposomes have been investigated as delivery vehicles for some time, but their approval and commercialization has encountered many obstacles during the past two decades of their development (17,18). In August 1997, FDA approved AmBisome (NeXstar Pharmaceuticals, Boulder, CO), a liposomal formulation of the water-insoluble drug amphotericin B, which has been commercialized. Other agency-approved liposomal formulations such as Doxil (Sequus, Menlo Park, CA) and DaunoXome (NeXstar Pharmaceuticals) contain water-soluble doxorubicin and daunorubicin, respectively, entrapped in the aqueous core of the liposome.

Liposomes are only suitable for those water-insoluble drugs that can partition in the liposomal bilayers without disrupting them, thus restricting the drug:lipid ratio. For example, the drug:lipid

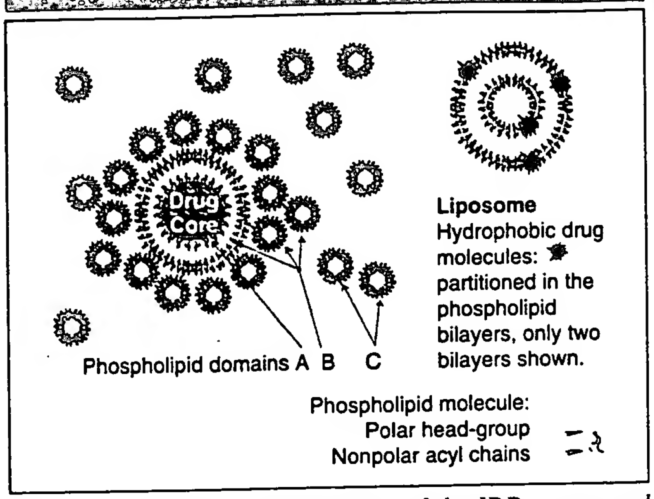

Figure 1: *A schematic representation of the IDD system and liposome.*

ratio of AmBisome is only 1:7 w/w and, with other excipients, results in a drug payload of only 37.7 mg amphotericin B per gram of formulation (derived from AmBisome product insert).

Mononuclear phagocytes — also known as the reticuloendothelial system (RES) — in the liver, lung, and spleen rapidly clear i.v. injected liposomes from circulation (19,20). Therefore, liposomes can serve as good vehicles for diseases of the RES. However, the preferential uptake of liposomes by the RES renders them less effective for diseases of other tissues. Liposomal formulations can also be toxic to RES components because of the high degree of accumulation of the drug and lipid in these compartments. To considerably decrease RES uptake of liposomes and increase their circulation time, certain glycolipids can be included, or the liposomes can be modified into so-called sterically stabilized or stealth liposomes (21–22).

Other systems of water-insoluble drug delivery include nanospheres and lipid complexes (23–25). Nanospheres are solid particles, ranging in size from 50 nm to several microns, that incorporate a drug through dissolution, encapsulation, or entrapment in a polymer matrix. As for liposomes, nanospheres usually have low drug payloads and are limited by the attainable efficiency of drug incorporation into the matrix. Lipophilic drugs also have been formulated as lipid complexes, and FDA has approved some of these formulations (25).

IDD TECHNOLOGY

IDD technology is a novel approach that is designed to combine the most favorable characteristics of emulsion and suspension technologies to provide a safe, stable, and high-payload drug delivery system (26,27). IDD technology (formerly MicroDroplet and MicroCrystal technologies) is believed to be the first application of delivering undiluted or highly concentrated drug substances as micron- or submicron-sized particles of the liquid or solid drug stabilized with physiologically safe, tissue compatible, and pharmaceutically acceptable surface modifiers such as natural and synthetic bipolar lipids (26,28). Similar delivery systems using these principles have subsequently been described (29–32). This technology has been applied to the formulation of insoluble drugs across many therapeutic classes and in the development of sustained- and immediate-release formulations. The surface-stabilized particles, typically <1 μm in size, are considered safe for parenteral administration because they are much smaller than red blood cells, which are ~7 μm. Two separate subtechnologies of IDD allow application to both solid and liquid (oily) drugs: MicroParticle and MicroDroplet technologies.

MicroParticle (formerly known as MicroCrystal) technology involves stabilizing submicron particles of a solid drug with either natural or semisynthetic phospholipids (28). It is likely that a monolayer of the hydrophobic phospholipid acyl chains sequesters the solid drug within the core. This core is believed to be further surrounded by additional phospholipid layers and vesicles. The same principle of phospholipid encapsulation is also applied to MicroDroplet technology. However, instead of solid drug particles, this technology uses an oily drug or droplets of a hydrophobic carrier in which the drug is dissolved. Again, the MicroDroplet is surrounded by phospholipid bilayer structures. It is believed that, depending upon the nature of the oily drug, some phospholipid dissolves in the drug core.

Figure 1 shows the IDD system in detail. The technology consists of a submicron-sized, water-insoluble drug core stabilized with a phospholipid surface modifier. Three distinct phospholipid domains are thought to exist in the MicroDroplet and MicroParticle formulations. The phospholipid molecules of domain A are considered closely associated with the drug core. This domain may consist of the phospholipid molecular coating on the drug core, either in a random order or in an organized monolayer. Domain B can consist of additional bilayers and/or small unilamellar vesicles loosely associated with the core. X-ray diffraction of MicroParticle formulations shows that multiple phospholipid bilayers, typical of multilamellar liposomes, appear to be absent in this domain. Domain B moves with the drug core and gives the particle its hydrodynamic size. Domain C comprises small bilayer vesicles and/or other phospholipid microstructures freely dispersed in the aqueous vehicle. A small fraction of the formulated drug may remain partitioned in the phospholipid structures of domains B and C. In the case of MicroDroplet formulations, depending on the phospholipid solubility in the liquid drug, a small amount of phospholipid may be dissolved in the lipophilic liquid drug core.

Liposomes are phospholipid bilayer vesicles. Lipophilic drugs are usually formulated with multilamellar vesicle liposomes consisting of many concentric bilayers (only two bilayers are shown in Figure 1). A small amount of the lipophilic drug molecule is incorporated in the phospholipid bilayers that are separated with aqueous medium.

PHYSICOCHEMICAL CHARACTERISTICS

IDD technology is thought to depend mainly on the hydrophobic interaction between the acyl chains of phospholipid monolayer and the drug surface. The presence of the phospholipid is essential to the formation as well as the stabilization of these formulations. High shear, cavitation, or impaction (e.g., milling, attrition, homogenization, and microfluidization) are used to reduce the drug particle size. To produce the IDD particles, these processes are carried out in the presence of phospholipids that associate at the freshly generated drug surface. This technique provides a capsule that prevents aggregation during size-

Table II: Drug partitioning in the MicroParticle formulation.

F rmulati n	Particle Size (nm) (V lume Weighted Mean)		Drug C ntent (%)	
	Formulati n	Supernatant	Supernatant	Sedim nt
1: drug 5% w/w, egg lecithin 10% w/w	2400	29	12.1	87.9
2: drug 5% w/w, egg lecithin 10% w/w	3900	30	10.7	89.3
3: drug 5% w/w, egg lecithin 10% w/w	2400	35	10.9	89.1
4: drug 10% w/w, egg lecithin 3% w/w	1800	27	1.7	98.3
5: drug 10% w/w, egg lecithin 3% w/w	1100	30	1.4	98.6

MicroParticle–cyclosporine formulations with egg lecithin (Pfanstiehl, Waukegan, IL) were prepared by microfluidization (formulations 1–3) or homogenization (formulations 4 and 5) at 18–20,000 psi. One 1-mL sample of each formulation was centrifuged for 10 min at ~15,000 *g* and ambient temperature. Volume weighted mean particle size of the formulation before centrifugation and that of the supernatant after centrifugation were determined. HPLC assay of the drug in the original formulation and the supernatant was performed to obtain the drug content.The fraction of drug present in the supernatant was thought to be associated with the nonsedimentable phospholipid microstructures, which are more likely to be of the measured size of less than ~50 nm. The remaining amount of drug in the sediment, ~90–99% of the total drug, is believed to be the core of the MicroParticle formulation.

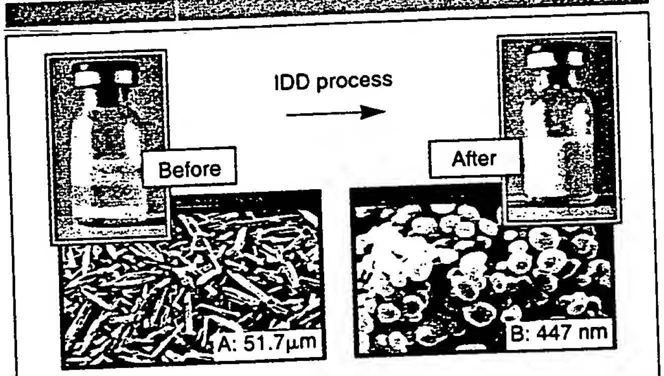

Figure 2: *IDD micronization: The electron micrograph, panel A, shows 50–100 μm particles of the native model drug (distance between the markers is 51.7 μm). The process yields phospholipid stabilized drug particles of ~500 nm, as shown in the electron micrograph, panel B (distance between markers is 400 nm).*

reduction processes and aggregation and/or crystal growth during the product's shelf life.

Figure 2 shows the crystals of a model drug and the particles harvested from the suspension of a MicroParticle formulation as observed under an electron microscope. The particles were reduced from ~100 μm to ~500 nm, resulting in a very homogeneous and stable formulation. Depending on the drug, MicroParticle formulations are stable in suspension. Alternatively, formulations can be dried to improve storage stability and ease of handling. Properly dried MicroParticle formulations of drugs reconstitute to their original particle size.

The use of phospholipids tends to invite a comparison between this technology and liposomes. However, liposomes are quite different from the MicroParticle and MicroDroplet formulations (see Figure 1). The predominant distinction is that the particles or droplets contain a core that primarily consists of drug, whereas in liposomes the lipophilic drug is dissolved in the lipid bilayers.

In a separate article, the authors will propose a structural model of surface-stabilized particles based on fluorescence microscopy observations, particle sizing by dynamic light scattering, X-ray diffraction experiments, and calculations on the distribution of phospholipid molecules. This model assumes that the phospholipid domains A, B, and C exist as described previously. Domain A consists of the phospholipid monolayer. Domain B, which determines the hydrodynamic radius of the particle, may contain a few more bilayers of phospholipid, small unilamellar vesicles, and/or other phospholipid microstructures (e.g., micelles or mixed micelles) surrounding the cyclosporine drug core. As described previously, these microstructures may remain loosely associated with the core and move with the drug particle. Domain C consists of small unilamellar vesicles and/or other phospholipid microstructures of <50 nm in diameter that are not associated with the drug core and move freely in the aqueous medium. Data shown in Table II indicate that

- almost all of the drug material is sequestered in the core of the MicroParticle or MicroDroplet
- a small fraction of the drug may be partitioned in the phospholipid microstructures smaller than ~50 nm. The drug fraction in this compartment depends on drug type, its solubility in the phospholipid, and the amount of phospholipid used in the formulation. Measurements of various MicroParticle preparations indicate that as much as ~10% of the drug can remain associated with these microstructures, which cannot be sedimented by moderate centrifugation.

Interaction between drug and phospholipids. The association of phospholipid with the drug surface originates primarily from an attractive hydrophobic interaction between the hydrophobic tails of the phospholipid molecules and the drug surface. Hydrophobic interaction between the drug surface and the acyl chains of the phospholipid molecules is possible because of the hydrophobicity of water-insoluble drugs. This interaction allows the sequestering of the drug within the MicroParticle without the solubilization in organic solvents that is required for preparing liposome, nanosphere, and emulsion systems.

Determinations of the phase transition temperature associated with the phospholipid structures in the IDD formulations have shown that minimal (if any) chemical interaction exists between the phospholipid sheath and the drug core. For instance, studies with water-soluble dyes showed that with dimyristoyl and dipalmitoyl lecithin coating, the MicroDroplets underwent thermal phase transitions similar to those observed when these

Table III: Fluorine 19–NMR chemical shift of MOF in different formulations.*

Composition	Fluorine 19–NMR Chemical Shift of MOF (ppm)	Change in Fluorine 19–NMR Chemical Shift from Pure MOF (ppm)
Pure MOF	−11.9	0
5 mL MOF + 2.0% egg PC	−11.8	−0.1
Water-saturated MOF	−11.9	0
MOF-saturated water	−18.4	+6.5
MicroDroplet MOF (6.7% MOF + 2.7% egg PC)	−11.79	−0.11
MOF-saturated liposomes	−11.25	−0.65
SDS micelles (38% SDS + 2.2% MOF)	−11.49	−0.41

*Data were taken from reference 35.

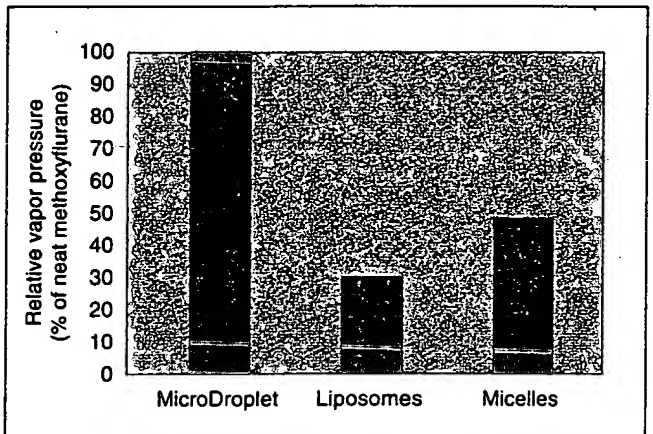

Figure 3: *Effect of formulation on the vapor pressure of MOF: vapor pressure of MOF does not change upon MicroDroplet formulation, but it is reduced to almost 30 and 50% in liposomal and micellar formulation, respectively (35).*

phospholipids were studied in pure form (e.g, lipid bilayers or liposomes) (33). These results suggest the presence of a phospholipid palisade structure in MicroDroplet formulations and negligible perturbation of the phospholipid interactions in this structure (34).

Results of fluorine 19–NMR chemical shift experiments also showed a lack of a strong interaction between the phospholipids and the drug entities in these formulations (35). The difference in the fluorine 19–NMR chemical shift of pure methoxyflurane (MOF), an anesthetic agent, and that of its MicroDroplet formulation (MOF plus egg phospholipid or water-saturated MOF) was almost negligible (see Table III). This observation suggests an almost identical microenvironment of MOF molecules in these conditions as well as the absence of any chemical interaction. However, a significantly different chemical shift of MOF in MOF-saturated water or in liposomal or micellar MOF formulations indicate that MOF molecules are highly perturbed in these media (see Table III) (35). Similarly, the MOF vapor pressure over its MicroDroplet formulation was very close to that of MOF itself. Conversely, liposomal and micellar formulations produced much lower MOF vapor pressures, indicating absence of strong drug–vehicle interaction in the MicroDroplet–MOF formulation (see Figure 3) (35).

PHARMACEUTICAL CHARACTERISTICS

IDD technology has broad applications to a variety of water-insoluble and poorly soluble drugs because it relies on the insolubility of the drug and its surface properties.

Payload. MicroDroplet and MicroParticle formulations can provide drug payloads as high as 200 mg/mL (see Table IV) (36). Drug:lipid ratios as high as 5:1 w/w have been achieved in a MicroParticle formulation of itraconazole, a triazole–antifungal drug. This ratio is very high compared with that of lipid–vehicle based formulations of another antifungal drug, amphotericin B (AmBisome, 0.14:1 w/w), and with Abelcet (The Liposome Co., Princeton, NJ) and Amphotec (Sequus), both of which have a 1:1 w/w ratio (data derived from product inserts). The inner core of the MicroParticles and MicroDroplets contains essentially pure drug material. This configuration can produce high payloads, which reduce the time and volume of formulation needed to inject the required dose. For example, in malignant hyperthermia a rapid i.v. administration of ~600 mL of a reconstituted commercial dantrolene formulation is required to treat an 80-kg adult. In comparison, the dosage of a MicroParticle formulation can be as low as 10 mL, with a concomitant reduction in injection time (37–39).

Stability. Depending on the drug, these formulations can display excellent physical and chemical stability. For example, after MicroDroplet formulations of propofol were subjected to a series of potentially destabilizing stresses including centrifugation, shaking, and thermal cycling, the fomulation did not appear to be significantly altered in appearance and particle size. Results of a current study of MicroDroplet formulations of propofol show physicochemical stability at various storage temperatures between 2–8 and 40 °C over a period of more than one year.

Table V shows that the change in particle size in the MicroParticle–itraconazole formulation was negligible after the formulation was subjected to various stress conditions including freeze–thaw, thermal cycling between 2–8 and 40 °C, shaking, sedimenting by centrifugation, and lyophilization followed by reconstitution.

Microparticulate suspensions can suffer from aggregation and sedimentation of the particles. Physical forces that lead to these suspension-destabilizing phenomena in pharmaceutical formulations, as well as their control, have been discussed in the literature (40,41).

Microparticulate suspensions also are known to undergo crystal growth during storage by a mechanism called "Ostwald ripening." Because small particles have a higher surface energy per

Table IV: Drug payloads of some commercial and IDD parenteral formulations.

Drug	Water Solubility*	Commercial Formulations**			Drug Payload in IDD Formulation (mg/mL)†
		Strength (mg/mL)	Brand Name	Manufacturer	
Carbamezapine	>10,000	Parenteral formulation not available			150
Dantrolene	100–1000	0.33	Dantrium i.v.	Procter & Gamble	200
Dexamethasone	>10,000	4–20	Decadron	Merck	100
Indomethacin	>10,000	0.5–1.0	Indocin i.v.	Merck	50
Oxytetacycline	1000–10,000	50–125	Terramycin	Roerig	200

* Units are parts of water required for one part of drug. Data were compiled from *USP 23/NF 18*, pp. 2116–2122.
** Data were compiled from *AHFS Drug Information*, G.K. McEvoy, Ed. (American Hospital Formulary Services, Bethesda, MD, 1997).
† From reference 36.

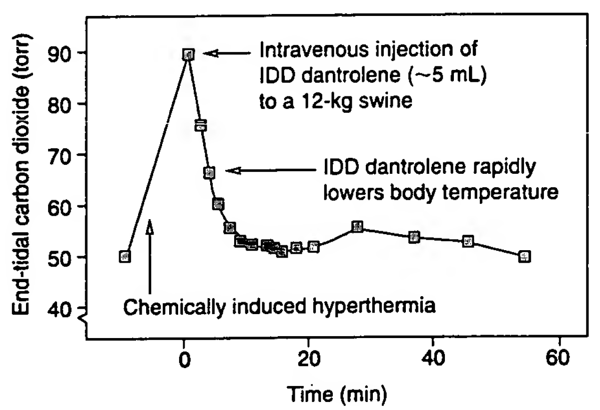

Figure 4: *In vivo immediate release of MicroParticle–dantrolene: Dantrolene is rapidly released from the MicroParticle formulation. Approximately 5 mL of MicroParticle–dantrolene was administered intraveneously to swine under chemically induced hyperthermia. The body temperature was rapidly lowered as indicated by the end-tidal carbon dioxide (38).*

unit mass than do large particles, molecules migrate from the surface of small particles to large particles, resulting in the growth of large particles and the disappearance of small particles. Therefore, the smaller the particles and the wider the particle-size distribution in the suspension, the greater the effect. Ostwald ripening has been minimized in MicroParticle formulations. For instance, no evidence of crystal growth was found in a MicroParticle–itraconazole formulation during storage, freeze–thaw, and thermal cycling stresses (see Table V).

Aggregation can also occur as a result of the excessive amounts of charged entities either in the suspension medium or on the particle's surface. Indeed, aggregates have been observed under optical microscopy in some stressed MicroParticle formulations. The addition of high concentrations of phosphatidyl ethanolamine, phosphatidic acid, phosphatidyl serine, or divalent cations to the suspension medium has been found to induce aggregation (34). Likewise, dilution of some MicroParticle formulations in normal saline caused the aggregation of particles, although such aggregation was not observed upon dilution of the same formulation in 5% aqueous dextrose.

Lyophilization and resuspension. In cases in which liquid suspensions of MicroParticle formulations display instability over extended periods of time, lyophilization can maintain particle size upon reconstitution. Results shown in Table V indicate that freeze-drying followed by reconstitution maintains particle size without adversely affecting the characteristics of MicroParticle formulations. Traditional cryoprotectants were added to the formulation to protect the microstructure of MicroParticle formulations during lyophilization. To enhance the flow properties of the powder and thus ensure ease of handling and reconstitution, other pharmaceutically acceptable excipients were also added. A lyophilized MicroParticle–busulfan formulation for i.v. administration has been developed that easily reconstitutes with water for injection (42).

Sterilization. Depending on the drug and the stability of the formulation, these phospholipid-stabilized suspension formulations can be terminally sterilized by heating at 121 °C or by γ irradiation. Lyophilized formulations using saturated phospholipids, e.g. MicroParticle–busulfan, can be successfully sterilized by γ irradiation without any degradation of the formulation or its components. In addition, certain MicroDroplet formulations can be filter sterilized. The authors have shown that neither method adversely affects stability (unpublished data).

Pharmacokinetics. The physical characteristics of each component in the formulated suspension allow the pharmacokinetics and drug-release mechanism to be controlled for application to both sustained- and immediate-release requirements. For example, a MicroDroplet–MOF formulation can produce ultralong duration of local anesthesia for a period of 3–8 days in rats and in humans upon intradermal injection (43,44). In contrast, i.v. injected MicroParticle–dantrolene is released rapidly to counteract hyperthermia within minutes and is completely eliminated from the bloodstream within 24 h (see Figure 4) (37–39).

The pronounced effect of RES clearance of colloidal drug carriers on pharmacokinetics has been well documented (19,20,45,46). In these systems, the nature and quantity of the excipients or surface modifier affects the drug clearance. As mentioned previously, preferential uptake of liposomes by the RES can be decreased by the use of certain glycolipids and steric stabilizers (21,22). In the case of nanospheres, although high surface charge can facilitate a dispersion's stability, it can also lead to faster clearance from the bloodstream by the RES

Table V: Particle size stability of a MicroParticle–itraconazole formulation under various conditions.

Stress Condition	Cycle	Appearance	Volume Weighted Particle Size (µm) Mean	90%	99.9%
Formulation before stress	0	Homogeneous suspension (HS)	1.04	1.60	2.52
Freeze–thaw*	4	HS	1.05	1.61	2.53
	10	HS	1.03	1.57	2.47
Thermal cycling**	2	HS	1.02	1.56	2.47
	4	HS	1.03	1.59	2.76
Shaking†	Day 3	HS	1.05	1.64	2.83
	Day 7	HS	1.06	1.68	2.83
Lyophilization–reconstitution††	A	HS	1.03	1.59	2.51
	B	HS	1.10	1.71	2.51
Sedimentation stress§	Before centrifuging	HS	1.05	1.58	2.48
	2000 rpm	Little sediment/easy resuspension	1.02	1.51	2.39
	3000 rpm	Little sediment/moderate resuspension	0.99	1.47	2.20
	6000 rpm	Significant sediment/difficult resuspension	0.99	1.46	2.17

* The formulation was frozen at −20 °C for 6 h, then thawed at ambient temperaure for 1 h. The particle size was measured at the end of each cycle. Only the values of representative cycles are shown.
**The formulation was stored for 24 h at 4 °C followed by 24 h at 40 °C. The particle size was measured at the end of each cycle. Only the values of representative cycles are shown.
†The formulation was shaken in vials by placing horizontally on an orbital shaker (~100 rpm) at ambient temperature. The particle size was measured every other day. Only the values of representative time points are shown.
††Cycle A: prelyophilization particle size of terminally heat-sterilized product. Cycle B: particle size after lyophilization and reconstitution.
§ The formulation was centrifuged for 15 min at the indicated speeds at ambient temperature. After each cycle the formulation was inspected for sedimentation and ease of resuspension. Resuspendibility: A few gentle strokes by hand needed to resuspend the formulation was considered "easy," vigorous shaking by hand was considered "moderate," and vortex mixing was considered "difficult." Particle size of the resuspended formulation was measured.

(46). Studies have shown that particles with low surface charge take longer to be cleared by the RES (46). In contrast, no evidence has been found of preferential uptake of microparticle formulations with the drugs that have been studied thus far. This characteristic allows the formulations to be used in immediate-release applications, as described in the following section.

Immediate therapeutic effect: i.v. injection of IDD formulation. Drug particle size and solubility in body fluids at the injection site largely determine the pharmacokinetics of parenteral suspensions (the larger the particle size, the slower the dissolution rate). Administration of the solubilized drugs (e.g., in cosolvents, in acidic or alkaline pH medium, or sequestered with agents such as β-cyclodextrin) can cause uncontrolled precipitation in body fluids and form potentially dangerous large particles with unpredictable dissolution behavior (5). However, MicroParticle formulations that consist of stabilized submicron particles allow rapid dissolution in body fluids upon injection. In vitro experiments that tested the release of piroxicam have shown that the majority of the drug is released very rapidly from the MicroParticle–piroxicam formulation in plasma (see Figure 5). Such a fast release of the drug in plasma would result in immediate release and rapid clearing upon i.v. administration. Similar results have been shown with MicroParticle–dantrolene, MicroParticle–flurbiprofen, and other drugs via i.v. injection into laboratory animals (see Figure 4) (37–39,47).

A recent study of rats and mice demonstrated rapid onset of action and high efficacy following i.v. injection of a MicroParticle formulation of water-insoluble felbamate (48). This injection displayed a rapid onset of action against maximal electroshock-induced tonic extension and reached its maximum efficacy several times faster than either orally or intraperitoneally administered drug. The results of this study suggest that par-

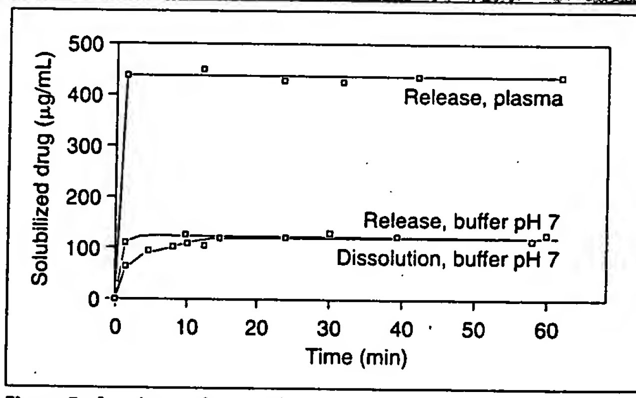

Figure 5: *In vitro release of MicroParticle–piroxicam: Release of piroxicam from its MicroParticle formulation is almost instantaneous and complete. A sample of the formulation was mixed with human plasma under gentle stirring at 37 °C. All of the available drug in the formulation released within 1 min. (top curve). The drug was released from the IDD formulation to its solubility limit in a buffer, pH 7 (middle curve). The release from IDD–piroxicam in human plasma or buffer was much faster than the dissolution process of the native drug crystals (bottom curves).*

enterally administered MicroParticle–felbamate is effective in an established model of generalized tonic-clonic seizures. It is proposed that this formulation is suitable for managing status epilepticus and in patients with highly refractory seizure disorders (48).

Sustained therapeutic effect. The physical characteristics of the drug, the concentration of the drug in the formulation, and the site of injection are major determinants of the overall in vivo pharmacokinetic behavior of IDD formulations. For example, solubility in water, oil–gas partition coefficient, and vapor pressure of anesthetic agent appear to be effective indicators of the therapeutic effect of certain formulations. Table VI compares these effects for MicroDroplet–MOF and MicroDroplet formulations of other anesthetics. When 6.7% MicroDroplet–MOF was injected intradermally, an ultralong duration of local anesthesia of 23 h was observed. However, diethyl ether — which has a higher water solubility, higher vapor pressure, and a lower oil–gas partition coefficient than MOF — had a local anesthetic effect for only 0.25 h when injected intradermally as a 7% diethyl ether MicroDroplet formulation. Also, diluting the anesthetic with additional mineral oil in the MicroDroplet formulation decreased the vapor pressure with a concomitant increase in drug-release rate from the MicroDroplet and produced a shorter anesthetic effect (34). Although the added diluent in the oil phase of the MicroDroplet formulation modulated the pharmacokinetics and efficacy (e.g., of MOF), the properties of phospholipid acyl chains of the MicroDroplet–MOF formulations do not appear to have such a major influence (34). The kinetics of anesthesia and the dose-response curves for MicroDroplet–MOF prepared with either egg or soybean lecithin are similar. This observation may be a result of the weak hydrophobic interaction of the phospholipid molecules with the drug entities, as mentioned previously.

The extent and level of therapeutic effect is further determined by the drug concentration in the formulation and the quantity of drug bound by tissues surrounding the injection site. Because safe and tissue-compatible excipients can be used and very high drug payloads can be produced, a large depot of the drug can be injected, resulting in prolonged therapeutic effects. This has been demonstrated with MicroDroplet–MOF and MicroParticle–nifedipine formulations (49). It is believed that a high oil–gas partition coefficient of the anesthetic agent and, in general, high lipid solubility increase a drug's ability to associate with cell membranes and other hydrophobic pockets surrounding the depot of administration. Once the surrounding tissues are saturated with drug, excess drug from the depot enters into the capillary bed and is removed by capillary streaming. The quantity of drug freely available upon injection thus determines the level of drug that is therapeutically active. The high payload of the IDD formulations and their tissue-compatible excipients allow the delivery of a quantity of water-insoluble drug to achieve a steady release of drug and a long therapeutic effect.

SAFETY AND REGULATORY ISSUES

The use of harsh excipients and extreme pH solutions is a major cause of irritation in traditional delivery methods. The IDD formulation approach eliminates these side effects through the use of phospholipids. Most phospholipids are accepted by regulatory agencies for parenteral and oral administration because of their endogenous nature in mammalian systems and their history of use and safety. These characteristics lead to formulations that have toxicities comparable to the native drug and are highly tissue compatible.

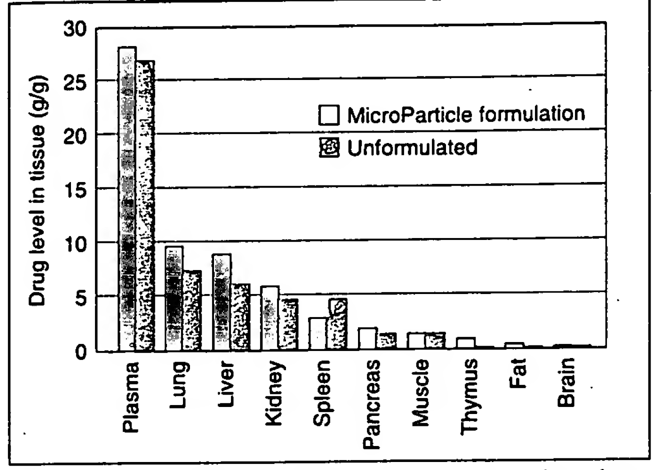

Figure 6: *Tissue distribution of MicroParticle–flurbiprofen: Almost identical tissue distribution profile of flurbiprofen is observed in rats upon i.v. administration of either MicroParticle–flurbiprofen or unformulated drug (n = 10 per group). MicroParticle–flurbiprofen formulation (5 mg/mL) in 20 mM phosphate buffer (pH 6.5) was prepared using a microfluidizer. This formulation was injected to ether-anesthetized rats via tail-vein at a dose of 10 mg/kg. Similarly, the unformulated drug was injected as 5 mg/mL solution in aqueous sodium carbonate, pH 10.2, at the same dose. In addition to plasma, nine different tissues were removed after 2 h and assayed by HPLC.*

A MicroParticle–busulfan formulation has been developed that allows i.v. dosage, provides predictable pharmacokinetics, and reduces the incidence of veno-occlusive disease and other toxicities (42). Comprehensive toxicology studies in rats and dogs using i.v. MicroParticle–busulfan showed no major safety concerns. This MicroParticle–busulfan formulation has successfully completed Phase I and Phase II clinical trials. Preclinical and clinical studies involving a MicroParticle formulation of tetracaine (50,51) and MOF (43,44) reported minimal neuronal and tissue damage. An ultralong-acting 10% MicroParticle–tetracaine formulation caused the same level of tissue inflammation in rats as a 1% tetracaine solution that is currently being used clinically (52). Preclinical results in laboratory animal models have also shown dezocine to have excellent tissue compatibility upon intradermal injection of its IDD formulation (53).

Surface-stabilized microparticulate formulations have also been shown not to alter the tissue distribution of the native drug. This is in stark contrast to liposomes and nanospheres, which are known to be sequestered (along with the entrapped drug) in the liver, lungs, and spleen (19,20,45,46). It is believed that the phospholipid molecules of the surface-modified microparticulate formulations are readily stripped away when the formulation enters the bloodstream. This process allows the drug to establish its natural pharmacodynamic equilibria and nonspecific delivery to tissues. No significant difference between the tissue

Table VI: Sustained-release efficacy of MicroDroplet formulations of anesthetic agents*.

Anesthetic	Vapor Pressure (mm Hg)	Oil/Gas Partition Coefficient	Solubility in Water	Durati n (h)
6.7% MicroDroplet–MOF	24	950	Extremely low	23
3.3% MOF in 3.5% mineral oil	12	N/A	Extremely low	2.5
7% mineral oil	0	N/A	Extremely low	no anesthesia
6.7% isoflurane	99	94	Extremely low	2
6.7% halothane	243	220	Extremely low	2
7% diethyl ether	443	65	817 mM	0.33

Formulations of anesthetic agents described in this table were injected into the distal third of the tail. Local anesthesia duration was measured by decreased sensitivity to electrical stimuli. Data were taken from reference 34.

distribution of MicroParticle–flurbiprofen and unformulated drug has been observed (see Figure 6) (47). Similarly, MicroParticle–flurbiprofen exhibited i.v. pharmacokinetics almost identical to those of unformulated drug in rats (47).

Application of IDD technology in the delivery of sustained-release formulations also provides safe delivery of drugs that have been proven toxic in other delivery forms. This is a result of the possibility of a slow release of drug into the bloodstream, thus avoiding toxic concentrations. For example, a solution of 10% tetracaine caused a high mortality and morbidity in rats (a 60% death rate) and the development of wet gangrene in the remaining animals, but a MicroParticle–tetracain formulation at the same concentration resulted in no adverse effects (50). A pharmacokinetic study in rats with MicroDroplet–MOF has demonstrated minimal availability of the drug in the liver, thus minimizing the generation and buildup of nephrotoxic metabolites (54). This example demonstrates how injectable MicroDroplet formulations can be used to therapeutic advantage, introducing lipophilic drugs into a tissue at high local concentrations, reducing the total body burden of the drug, and allowing efficient drug removal (54).

CONCLUSION

The IDD delivery system has been shown to provide safe and stable injectable formulations of water-insoluble or poorly soluble drugs. It allows for delivery of high payloads of insoluble drugs by various routes of parenteral administration (sustained release through intramuscular, subcutaneous, or intradermal routes, and immediate release through the intravenous route). This technology possesses many advantages in terms of efficacy and safety compared with currently available delivery methods such as emulsions, liposomes, cyclodextrins, and nanospheres.

Because IDD technology relies on a drug's physical properties — such as its insolubility — rather than on its specific chemical properties, it can be applied to a broad range of insoluble drugs. Several water-insoluble drugs have been successfully formulated for parenteral administration and are currently under development. Researchers have achieved excellent reproducibility in the large-scale manufacture of these products without the major scale-up problems encountered with liposome formulations. Phase I and Phase II clinical trials have been completed on various IDD formulations, which have demonstrated excellent safety and efficacy profiles as well as a long shelf life. In addition to causing no side effects, these phospholipid-stabilized drug formulations have pharmacokinetics and tissue distribution profiles similar to those of the commercial formulation or the native drug. These characteristcs should facilitate the regulatory approval of drugs formulated with this drug delivery system.

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NEWS BRIEF

Respiratory drug delivery conference call for papers

The School of Pharmacy at Virginia Commonwealth University is accepting innovative research manuscripts for its Respiratory Drug Delivery VII (RDD VII) conference scheduled for 14–18 May 2000 in Tarpon Springs, Florida.

Research topics to be discussed at RDD VII include pulmonary pharmacokinetics and toxicokinetics; pharmacokinetics and pharmacodynamics of macromolecular and conventional drugs; new drugs, formulations, aerosol delivery technologies, and research techniques; formulation and processing issues; and regulatory science. The conference will also provide a suppliers forum and a scientific posters session.

Authors should submit a 100-word abstract by 30 June 1999 to Peter R. Byron, School of Pharmacy, Virginia Commonwealth University, PO Box 980533, Richmond, VA 23298-0533, tel. (804) 828-6377, fax (804) 828-8359, e-mail (rdd@hsc.vcu.edu).

Abstracts will be reviewed for originality, merit, and appropriateness, and authors will be contacted in August or September 1999.

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AUTHORS The 109 chapters of this edition of *Remington's Pharmaceutical Sciences* were written by the editors, by members of the Editorial Board, and by other authors listed on pages ix to xi.

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blood level may result. Fo[illegible]ample, drugs with short half-lives require frequent dosi[illegible]maintain constant therapeutic levels.

2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs give[illegible]conventional dosage forms by multiple-dosing can prod[illegible]the desired drug blood level for extended periods of time. Frequently, however, these problems are significant enough to make drug therapy with conventional dosage forms less desirable than sustained-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of sustained-release drug delivery systems. There are numerous potential advantages of sustained-release drug therapy that will be discussed in the next section.

Sustained-Release Drug Therapy

As already mentioned, conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments, and suppositories. For purposes of this discussion, these dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Absorption Pool} \xrightarrow[\text{absorption}]{k_a} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

The absorption pool represents a solution of the drug at the site of absorption, and the terms k_r, k_a, and k_e are first-order rate constants for drug release, absorption, and overall elimination, respectively. Immediate release from a conventional dosage form implies that $k_r \ggg k_a$ or, alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area. For nonimmediate release dosage forms, $k_r \lll k_a$, that is, release of drug from the dosage form is the rate limiting step. This causes the above kinetic scheme to reduce to the following:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a nonimmediate release delivery system must be primarily directed at altering the release rate by affecting the value of k_r. The many ways in which this has been attempted will be discussed later in this chapter.

Nonimmediate release delivery systems may be conveniently divided into four categories:

1. Delayed release
2. Sustained release
   a. controlled release
   b. prolonged release
3. Site-specific release
4. Receptor release

Delayed-release systems are those that utilize repetitive, intermittent dosings of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed-release systems include repeat action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating. A delayed-release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range, as shown in Fig 92-3, but nonetheless is more effective for patient compliance than conventional dosage forms.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful at maintaining constant drug levels in the blood or target tissue, it is considered a *controlled-release* system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a *prolonged-release* system. This is illustrated in Fig 92-4.

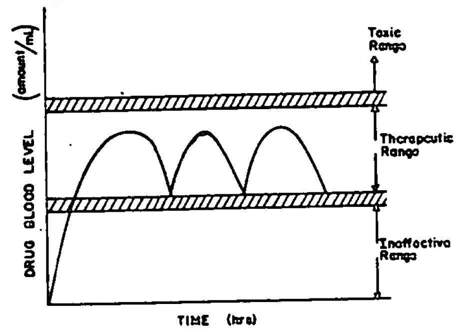

Fig 92-3. Typical drug blood level versus time profiles for delayed release drug delivery by a repeat-action dosage form.

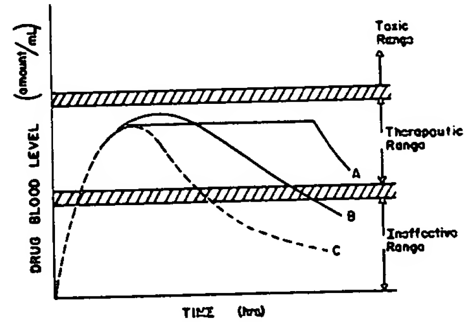

Fig 92-4. Drug blood level versus time profiles showing the relationship between controlled release (A), prolonged release (B), and conventional release (C) drug delivery.

Site-specific and *receptor release* refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue; for receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

Release Rate and Dose Considerations

Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal goal of a sustained-release delivery system. In fact, in some cases optimum therapy is achieved by oscillating, rather than constant, drug levels. An example of this would be antibiotic therapy, where the activity of the drug is required only during growth phases of the microorganism. A constant drug level will succeed at curing